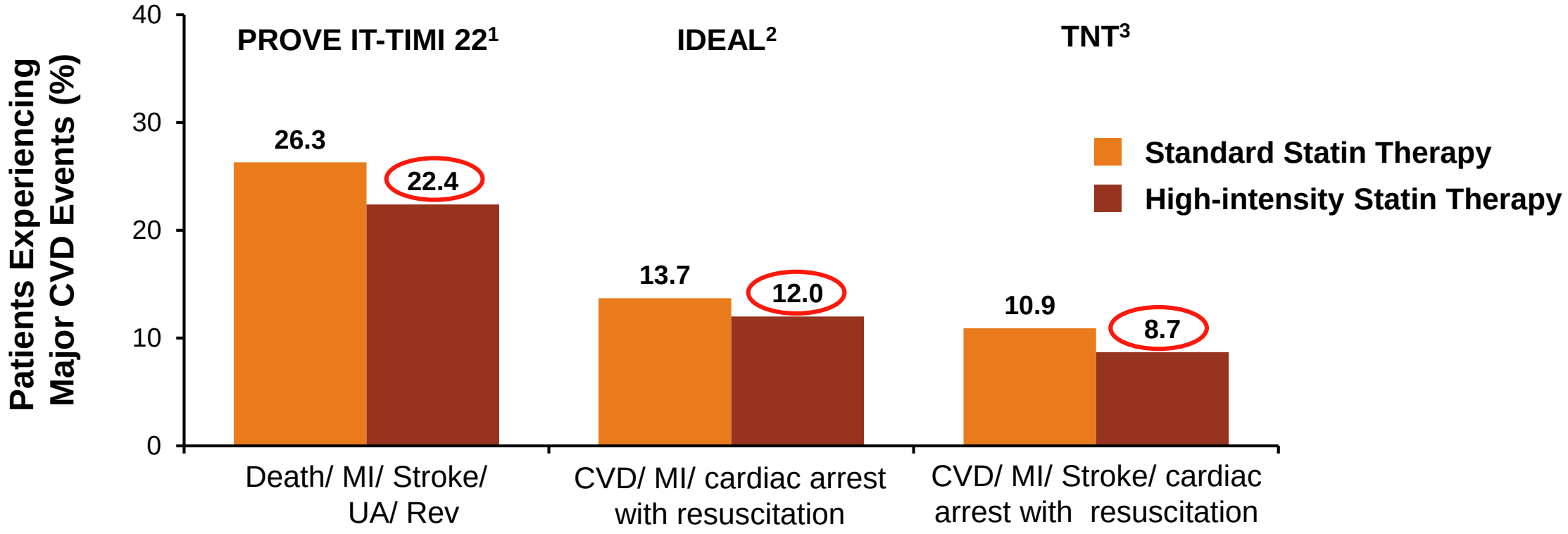
Learning Objectives

- Assess the safety and efficacy of PCSK9 inhibitors in reducing cardiovascular events in patients with acute coronary syndrome and hypercholesterolemia
- Appropriately integrate PCSK9 inhibitors in clinical practice to reduce the risk of cardiovascular events in high-risk patients
- Review current evidence and set optimal LDL-cholesterol targets for patients with documented ASCVD

Substantial Residual Risk Still Exists



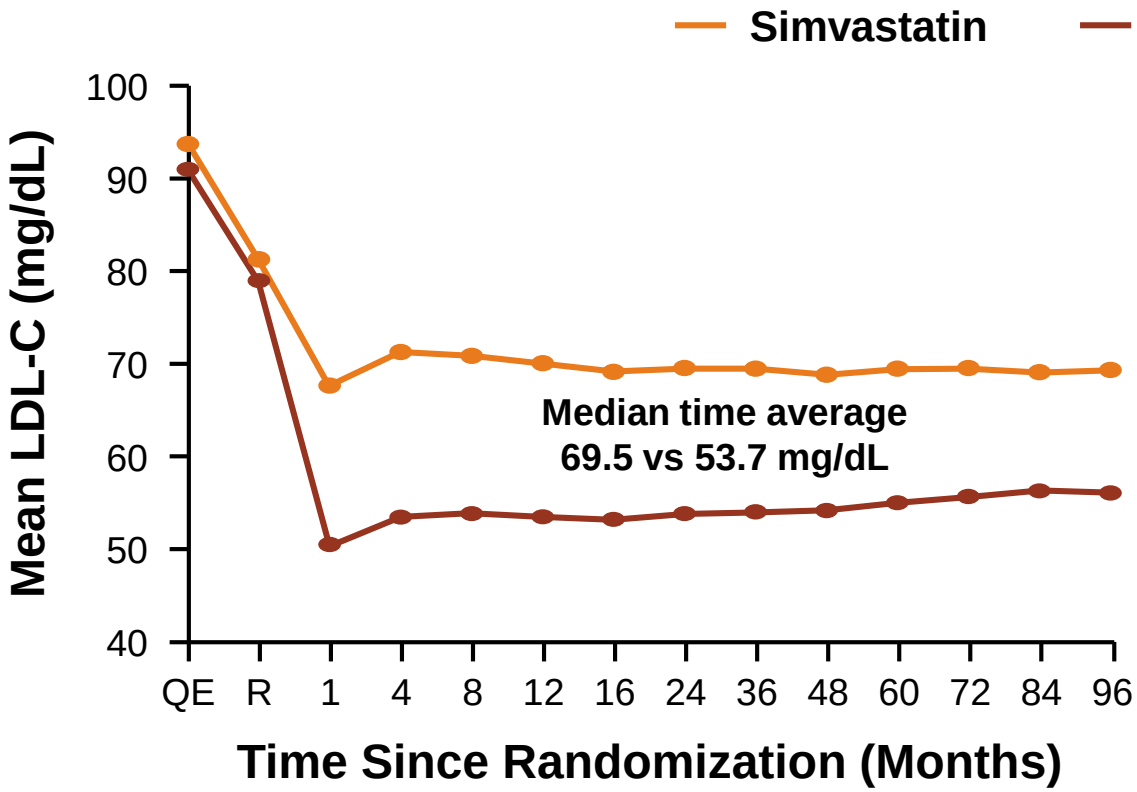
N	4162		8888		10,001	
LDL-C mg/dL	95	62	104	81	101	77

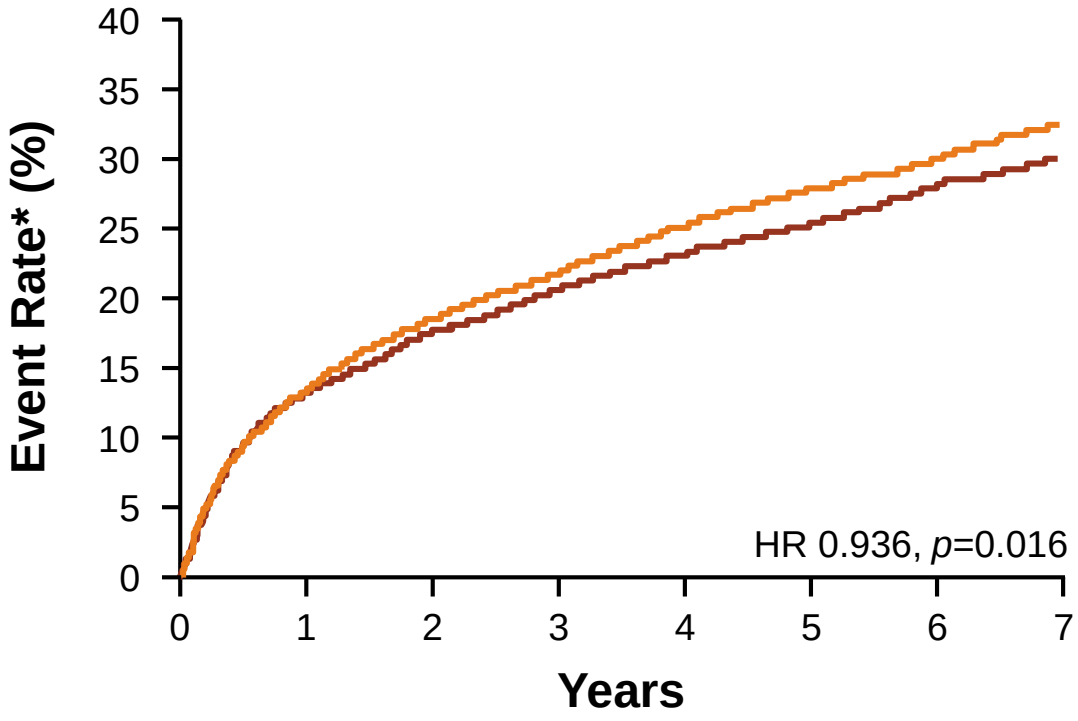
1. Cannon CP, et al. *N Engl J Med*. 2004;350(15):1495-1504. 2. Pedersen TR, et al. *JAMA*. 2005;294(19):2437-2445. 3. LaRosa JC, et al. *N Engl J Med*. 2005;352(14):1425-1435.

Impact of Ezetimibe in ASCVD

IMPROVE-IT Study

18,144 ACS patients randomized to simvastatin (40 mg QHS) or simvastatin/ezetimibe (40 mg/10 mg QHS) for seven years





***Composite of CV death, MI, unstable angina, coronary revascularization, or stroke.**
ACS = acute coronary syndrome; HR = hazard ratio.

Cannon CP, et al. *New Engl J Med* . 2015;372(25):2387-2397.

FOURIER vs ODYSSEY OUTCOMES

	Alirocumab (*N* = 9,462)[1]	Evolocumab (*N* = 13,784)[2]
Patient type	ACS patients (within 1–12 months of event)	ASCVD patients with history of MI, stroke, or symptomatic PAD
Time from index event to randomization	2.6 months	~3.3 years (MI or stroke)
High-intensity statin	88.6%	69.5%
Baseline LDL-C	87 mg/dL	92 mg/dL
Median follow up	2.8 years	2.2 years
Outcomes		
Primary endpoint[a,b]	0.85 HR *P* = 0.0003	0.85 HR *P* <0.001
Nonfatal MI	0.86 HR *P* = 0.006	0.73 HR *P* <0.001
Stroke	0.73 HR *P* = 0.01	0.79 HR *P* = 0.01
CVD	0.92 HR *P* = 0.38	1.05 HR *P* = 0.62
All-causes death	0.85 HR *P* = 0.026	1.04 HR *P* = 0.54

[a] Alirocumab = CVD, non-fatal MI, ischemic stroke, or UA requiring hospitalization; [b] Evolocumab = CVD, MI, stroke, hospitalization for UA, or coronary revascularization.

1. Steg PG. ACC 2018, Orlando, FL. 2. Sabatine MS, et al. *New Engl J Med.* 2017;376:1713–1722.

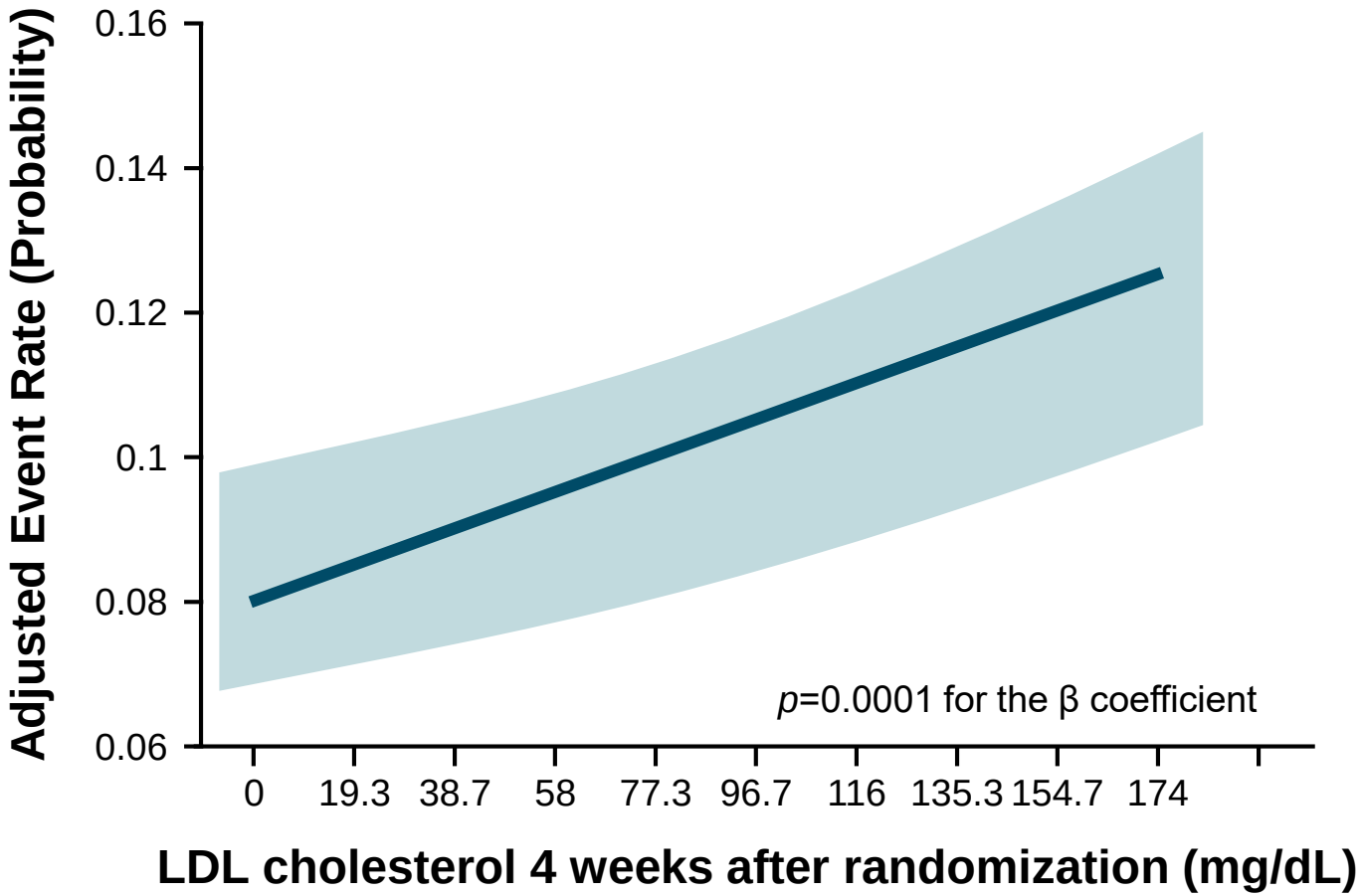
Impact of Lower LDL on Outcomes

Trial	Comparison	LDL Achieved (mean, mg/dL)	Outcomes	*p* Value
IMPROVE-IT[a]	Simvastatin vs. EZ / Simvastatin	70 vs. 54	34.7% vs. 32.7%	0.016
FOURIER[a]	Placebo vs. Evolocumab	92 vs. 30	11.3% vs. 9.8%	<0.001
ODYSSEY OUTCOMES[b]	Placebo vs. Alirocumab	93 vs. 38	11.1% vs. 9.5%	0.0003

***Median values; [a]CV death, MI, coronary revascularization, UA, or stroke; [b]CV death, MI, stroke, or UA requiring hospitalization.**

Cannon CP, et al. *N Engl J Med*. 2015;372(25):2387-97. Sabatine MS, et al. *N Engl J Med*. 2017;376(18):1713-1722. Steg PG, et al. Presented at: ACC.18 Scientific Sessions; March 10, 2018; Orlando, FL.

FOURIER – Lower CV Event Rates with Lower LDL-C Levels*, Even Down to 20 mg/dL

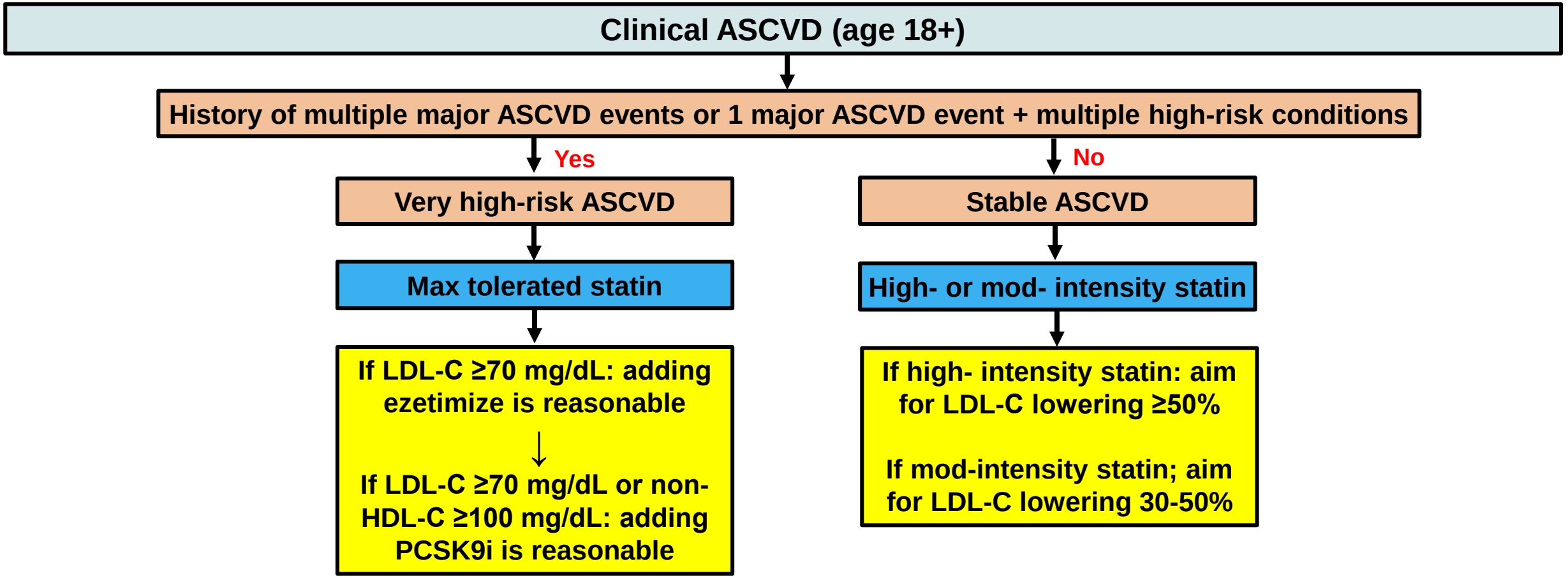


There were no safety concerns with very low LDL-cholesterol concentrations over a median of 2.2 years.

***Relationship between the achieved LDL-C concentration at 4 weeks and the risk of CVD, MI, or stroke.**

Giugliano RP, et al. *Lancet*. 2017 Aug 25. [Ahead of print]

2018 Cholesterol Guidelines
Secondary ASCVD Prevention



Grundy SM, et al. *J Am Coll Cardiol*. 2018 Nov 8. pii: S0735-1097(18)39034-X. [Epub ahead of print]

Key Takeaways

- While statins remain the standard for treatment of patients with ASCVD and hypercholesterolemia, non-statin therapies such as ezetimibe, alirocumab, and evolocumab offer additional options for reducing the risk of adverse CV events.
- ODYSSEY OUTCOMES and FOURIER have shown PCSK9 inhibitors alirocumab and evolocumab to be effective in lowering LDL-C and CV events in patients with ACS and stable ASCVD, respectively
- Achieving lower LDL levels (< 50 mg/dL) has been shown to be safe and significantly reduces the risk of cardiovascular events